added new claims 27 to 30. An Appendix including a marked-up copy of the amendments is attached, showing the changes. The attachment is captioned **"Version with markings to show changes made."** Former claims 2-26 are rejected under 35 USC §§ 112, 102 and 103. For the reasons outlined below, these rejections are respectfully traversed and reconsideration and withdrawal are respectfully requested.

## Rejections Under 35 USC § 112

The Examiner has rejected claims 2-26, arguing that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the invention. The Examiner has referred to page 17 of the specification (lines 3-10) thus concluding that "CGRP" encompasses any peptide from any organism which shares significant structural and functional homology with the calcitonin gene-related peptide. According to the Examiner, the applicant has only disclosed a mammalian CGRP, adrenomedullin and mammalian [Cys(ACM)$^{2,7}$]CGRP. During the October 4, 2001 interview of Examiner Nolan with Joy Morrow and Serge Shahinian of Smart and Biggar, Mr. Nolan noted that he considered it appropriate if the scope of the claims encompasses all known CGRP molecules.

In response, claim 21 has been amended to recite human and rat CGRP peptides and their [Cys(ACM)$^{2,7}$]CGRP forms, and claim 4 has been amended to recite human and rat CGRP peptides. Further, claims 4, 6 and 7 have been amended to depend from claim 21, and claims 3, 9 to 20, and 22 to 26 have been removed. Further, new claim 30 has been added which is similar to claim 21 and additionally recites other known CGRP peptides and their corresponding [Cys(ACM)$^{2,7}$]CGRP forms. Further, claim 21 has been amended to remove the term "adrenomedullin" without prejudice or disclaimer. In addition, new claim 27 has been added which depends from claim 4 and recites the α forms of human and rat CGRP peptides; and new claims 28 and 29 have been added which are similar to claims 4 and 27 but are directed to the corresponding linear analogs.

Applicant reserves the right to pursue any subject matter removed by these amendments in one or more continuation applications.

The amendments noted above are supported by the common general knowledge in the art, as described in for example a number of references cited in the application as well as in references cited therein. For example, Barnes et al., 1991 (reference 1; item A11 in the Information Disclosure Statement) notes that CGRP is a 37 amino acid peptide, of which two forms exist, α-CGRP and β-CGRP, differing by 3 amino acids (also noted in the bottom paragraph of page 5 of the disclosure). References cited therein mention CGRP peptides of various species, including human (refs. 205, 209, 210, 214, 217) and rat (refs. 206, 212). Further, it is known in the art that CGRP has been isolated, purified and characterized from human, rat, cow, pig, chicken and frog. It is also known that the effects of CGRP from different sources (including human and rat) have been studied in a number of species, including human, rat, guinea pig, dog, sheep, ferret, mouse, rabbit and pig. Various forms of CGRP are commercially available, including human, rat and chicken. Further, the common general knowledge in the art is reflected in various publications, such as the review of Zaidi et al.[1] (provided with Applicant's letter of November 14, 2001), which provides various details regarding CGRP. The Examiner is referred in particular to Table 3 on page 119 of Zaidi et al., which describes the structure of CGRP peptides of various species (utilizing the designations "1" and "2" rather than "α" and "β", respectively). Further, it is noted on for example page 5 (line 28) of the description where it is that CGRP can exist in two forms designated α- and β-CGRP. In further support of the above, please find enclosed a Declaration pursuant to 37 CFR 1.132, of applicant Alain Cadieux, which asserts that the following compounds were used in the studies presented in the application:

1. human α CGRP;
2. rat α CGRP;
3. the linear analog (acetoamidomethyl cysteine 2,7) of human α CGRP; and

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[1] Zaidi, M., et al. (1990) The Calcitonin Gene Peptides: Biology and Clinical Relevance. *Critical Reviews in Clinical Laboratory Sciences* 28(2): 109-174.

4. human adrenomedullin.

The Examiner is further referred to page 25 (line 17) of the description where it is noted that the studies described in the application were performed as described in references 4 and 7 (items A14 and A30, respectively, of the Information Disclosure Statement), which noted that human and rat α CGRP were used in these studies. In addition, other references cited in the application (e.g. Barnes et al. – see above) note the existence of α- and β-CGRP.

In light of the above, applicant respectfully requests that the rejection be withdrawn.

The Examiner has further rejected claims 2-26 pursuant to 35 USC § 112 based on the use of the term "prevention", arguing that the specification does not reasonably provide enablement for the method of prevention of the pathophysiological manifestations of the recited diseases. In response, applicant first wishes to note that claim 21 and dependent claims 2 to 20 do not recite the term "prevention" and therefore respectfully submits that the rejection is inapplicable with respect to these claims. Regarding claims 22 to 26, the applicant notes that claims 22 to 26 have been deleted as noted above. Therefore, in light of the above, the applicant respectfully requests that the rejection be withdrawn.

**Rejections Under 35 USC § 102**

The Examiner has rejected claims 2-26 as anticipated in light of United States Patent No. 5,858,978 as evidenced by *The Merck Manual*. In response, the applicant respectfully submits the following.

As discussed in applicant's letter of December 4, 2000, the '978 Patent only describes a relationship (observed ***in vitro***) between CGRP and an inhibition of IL-1, via a cAMP-mediated mechanism. The '978 Patent then further mentions in general terms a

relationship between cytokine release and inflammatory reactions and in turn recites a number of diseases which may involve inflammation, with asthma being one example of many such diseases. As noted in applicant's letter of December 4, 2000, numerous differences exist between the subject matter disclosed in the '978 Patent and the findings described in the instant application.

Applicant further wishes to note that the Examiner has referred to *The Merck Manual* to expand the definition of asthma beyond that recited in the '978 Patent. This combination of references is not believed to be appropriate under 35 USC § 102.

Furthermore, by such reference, it is assumed that the Examiner considers the information presented in *The Merck Manual* to reflect the general common knowledge of the art. In this regard, applicant notes that *The Merck Manual* also indicates, as is indeed generally known in the art, that CGRP is known to cause bronchoconstriction and airway obstruction (oedema, mucus secretion, etc.; see page 557, right column, last paragraph), which was in fact the state of the knowledge in the art prior to the instant applicant's findings. The instant applicant, alternatively, was the first to directly test the effects of CGRP on animal airways and thus discovered that its effects were precisely opposite to the conventional wisdom in the art. Therefore, while the Examiner apparently relies on *The Merck Manual* to expand the definition of asthma, the applicant respectfully submits that the Examiner fails equally to consider that *The Merck Manual* directly teaches against a use of CGRP for the treatment of asthma as allegedly disclosed in the '978 Patent.

Further, during the December 11, 2001 interview with Examiner Nolan the general state of the art was discussed with respect to CGRP. For example, Examiner Nolan noted that upon his review of Pinto *et al.* (1996, *British J. Pharmacol.* 119: 1477-1483; item A17 of the Information Disclosure Statement), conflicting results have been shown with regard to CGRP activity. Specifically, CGRP was shown to potentiate the cholinergic contractions of tracheal "rings". However, CGRP, when acting through a non-cholinergic mechanism was shown to reduce the excitatory response in bronchi.

Consistent with these observations, it is noted in the beginning of the "Discussion" of Pinto *et al.* (page 1480, upper right) that "the effects of CGRP on tracheobronchial smooth muscle are controversial" and several reports are cited which describe conflicting results in this regard. As such, in the absence of direct measurements of the effects of CGRP on airways challenged with various stimuli as performed by the instant inventor, the state of the art prior to the instant invention provides no guidance to one skilled in the art that CGRP may be used effectively for such a purpose.

Applicant respectfully submits that he was the first to recognize, demonstrate (including ***in vivo*** results) and describe the claimed activity for CGRP (namely in the reduction of agonist-induced bronchoconstriction and/or bronchospasm, allergen-induced bronchospasm, lung inflammation caused by increased eosinophilia and/or the reduction of airway hyperreactivity). Applicant has demonstrated that CGRP protects against a wide variety of bronchoconstrictor stimuli (e.g. substance P, metacholine, allergen challenge, etc.), and reduces bronchoconstriction, bronschospasm, eosinophil accumulation in the bronchial walls and bronchospastic airway responses such as reversible airway hyperreactivity. Further, applicant is the first to describe CGRP activation of the chemotaxis of eosinophils from the bronchial mucosa (see Example 3 [page 33, lines 13 to 15 in particular]). Therefore, claim 21 has been amended to recite a method for the reduction of agonist-induced bronchoconstriction and/or bronchospasm, allergen-induced bronchospasm, lung inflammation caused by increased eosinophilia, and/or airway hyperreactivity. This amendment is supported by, for example, pages 2 (lines 9-14), 15 (lines 27-29), 16 (lines 6-7), 26 (line 7) and 31 (lines 3-11). Further, claims 4, 6 and 7 have been amended to depend from claim 21 and thus incorporate the changes therein, and claims 3, 9 to 20, and 22 to 26 have been removed as noted above.

In light of the above, applicant respectfully submits that the claims as amended, which are directed to the reduction of agonist-induced bronchoconstriction and/or bronchospasm, allergen-induced bronchospasm, lung inflammation caused by increased cosinophilia or of airway hyperreactivity, are novel over the '978 patent. As such, applicant respectfully requests that the objection be withdrawn.

**Rejections Under 35 USC § 103**

The Examiner has rejected claims 2-26 as obvious in light of the '978 Patent discussed above in view of United States Patent No. 5, 510, 339. In response, the Applicant respectfully submits the following.

Based on the above comments relating to the novelty rejection in light of the '978 patent, applicant respectfully first submits that the features recited in the claims as amended are not disclosed in the '978 Patent. As such, applicant respectfully submits that a combination of these references in this regard is no longer applicable and respectfully requests that the rejection be withdrawn.

**Other Issues**

During the telephone interview of December 11, 2001, Examiner Nolan raised the issue of the article "Cadieux *et al.* (1999) Am. J. Respir. Crit. Care Med., 159:235-243" (item A30 of the Information Disclosure Statement). Specifically, Examiner Nolan noted that the authorship of this article is not identical to the applicants listed in the instant application, and requested the filing of a "Katz" declaration. Therefore, please find enclosed a further Declaration pursuant to 37 CFR 1.132 (incorrectly labelled as "37 CFR 1.131"), which asserts that Alain Cadieux is the sole inventor of the subject matter disclosed in the just noted article.

It is believed this responds to all of the Examiner's concerns, however if the Examiner has any further questions, he is invited to contact Joy Morrow at 613-232-2486. Further, If the Examiner does not consider that the application is in a form for allowance, an interview with the Examiner is respectfully requested.

Respectfully submitted,

April 26, 2002
Date

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

2. The method of claim 21, wherein said administration is via a pulmonary route.

3. [The method of claim 21, wherein said administration of said active agent is for the treatment of asthma.]

4. The method of claim [3]21, wherein said active agent is selected from the group consisting of human CGRP and rat CGRP.

5. The method of claim 4, wherein said administration is via a pulmonary route.

6. The method of claim [3]21, wherein said active agent has a purity of at least about 95 to 98%.

7. The method of claim [3]21, wherein said active agent is dispersed within a composition comprising a pharmaceutically acceptable excipient, liquid or solid carrier.

8. The method of claim 7, wherein said composition is in a form suitable to be introduced into a mammal by providing an aerosol or dry powder comprising said active agent for inhalation by said mammal.

9. [The method of claim 21, wherein said administration of said active agent is for the treatment of bronchospastic diseases characterized by airway hyperreactivy.]

10. [The method of claim 9, wherein said active agent is CGRP.]

11. [The method of claim 10, wherein said administration is via a pulmonary route.]

12. [The method of claim 9, wherein said active agent has a purity of at least about 95 to 98%.]

13. [The method of claim 9, wherein said active agent is dispersed within a composition comprising a pharmaceutically accceptable excipient, liquid or solid carrier.]

14. [The method of claim 13, wherein said composition is in a form suitable to be introduced into a mammal by providing an aerosol or dry powder comprising said active agent for inhalation by said mammal.]

15. [The method of claim 21, wherein said administration of said active agent is for the treatment of lung inflammatory reaction characterized by increased eosinophilia.]

16. [The method of claim 15, wherein said active agent is CGRP.]

17. [The method of claim 16, wherein said administration is via a pulmonary route.]

18. [The method of claim 15, wherein said active agent has a purity of at least about 95 to 98%.]

19. [The method of claim 15, wherein said active agent is dispersed within a composition comprising a pharmaceutically acceptable excipient, liquid or solid carrier.]

20. [The method of claim 19, wherein said composition is in a form suitable to be introduced into a mammal by providing an aerosol or dry powder comprising said active agent for inhalation by said mammal.]

21. A method for the [treatment] reduction of: [a disease selected from asthma, bronchospastic diseases characterized by airway hyperreactivity, and lung inflammatory diseases characterized by increased eosinophilia,]
(i) agonist-induced bronchoconstriction;
(ii) agonist-induced bronchospasm;
(iii) allergen-induced bronchospasm;
(iv) lung inflammation caused by increased eosinophilia;
(v) airway hyperreactivity; or
(vi) any combination of (i) to (v);
wherein said method comprises the administration of an active agent selected from the group consisting of: [CGRP, adrenomedullin and [Cys(ACM)$^{2,7}$]CGRP]
a) human calcitonin gene-related peptide (human CGRP);
b) rat CGRP;
c) diacetoamidomethyl cysteine form of (a) ([Cys(ACM)$^{2,7}$] human CGRP); and
d) diacetoamidomethyl cysteine form of (b) ([Cys(ACM)$^{2,7}$] rat CGRP).

22. [A method for the prevention or treatment of the pathophysiological manifestations of a disease selected from asthma, bronchospastic diseases characterized by airway hyperreactivity, and lung inflammatory diseases characterized by increased eosinophilia, wherein said method comprises the administration of an active agent selected form the group consisting of CGRP, adrenomedullin and [Cys(ACM)$^{2,7}$]CGRP.]

23. [The method of claim 22, wherein said administration is via a pulmonary route.]

24. [The method of claim 22, wherein said administration of said active agent is for the prevention or treatment of the pathophysiological manifestations of asthma.]

25. [The method of claim 22, wherein said active agent is CGRP.]

26. [The method of claim 22, wherein said pathophysiological manifestations are selected from the group consisting of:

(a) reversible airway obstruction,

(b) airway hyperreactivity, and

(c) lung inflammatory reaction characterized by increased eosinophilia.]

27. The method of claim 4 wherein said active agent is selected from the group consisting of human α CGRP and rat α CGRP.

28. The method of claim 21, wherein said active agent is selected from the group consisting of the diacetoamidomethyl cysteine form of human CGRP ([Cys(ACM)$^{2,7}$] human CGRP) and the

diacetoamidomethyl cysteine form of rat CGRP ([Cys(ACM)$^{2,7}$] rat CGRP).

29. The method of claim 28, wherein said active agent is selected from the group consisting of the diacetoamidomethyl cysteine form of human α CGRP ([Cys(ACM)$^{2,7}$] human α CGRP) and the diacetoamidomethyl cysteine form of rat α CGRP ([Cys(ACM)$^{2,7}$] rat α CGRP).

30. A method for the reduction of:

(i) agonist-induced bronchoconstriction;

(ii) agonist-induced bronchospasm;

(iii) allergen-induced bronchospasm;

(iv) lung inflammation caused by increased eosinophilia;

(v) airway hyperreactivity; or

(vi) any combination of (i) to (v);

wherein said method comprises the administration of an active agent selected from the group consisting of:

a) human calcitonin gene-related peptide (human CGRP);

b) rat CGRP;

c) cow CGRP;

d) pig CGRP;

e) chicken CGRP;

f) frog CGRP; and

g) diacetoamidomethyl cysteine forms of (a) to (f) ([Cys(ACM)$^{2,7}$]CGRP).